# Tumor Hypercalcemia

As EARLY AS 1855 CALCIUM abnormalities associated with tumors (ectopic calcification in patients with breast cancer) were described by Virchow.[1,2] In 1899 bone cysts not containing cancer were noted by Stephen Paget in women with breast cancer. This was probably the first suggestion of a humor from a tumor. Hypercalcemia was not associated with breast cancer until 1942. At first it was considered a complication of therapy, but it is now established that hypercalcemia occurs more frequently in the untreated patient and bears no relation to progression or regression of lytic lesions.

In 1961 Warwick et al[3] noted hypercalcemia in 9.1 percent of 438 patients with advanced cancer; however, the increased use of routine chemical screening may well yield a higher incidence today.

The hypercalcemia of malignancy is most commonly associated with osteolytic metastasis. Usually, the serum calcium and phosphate levels are both elevated. A rare cause of hypercalcemia by metastasis is destruction of the adrenal glands, resulting in Addison's disease. The occurrence of hypercalcemia with normal or elevated serum phosphate levels, in patients with or without osseous metastasis has been related to osteolytic compounds present in lipid extracts of tumors and serum. Contained in lipid extracts are phytosteryl esters which have vitamin D-like action on bone. Recently, the osteolytic compound found by Goldhaber in mouse sarcoma has been identified as prostaglandin $E_2$. Both $E_2$ and $F_2\alpha$ prostaglandins, which have osteolytic activity, also have been found in brochogenic carcinoma, a cancer in which hypercalcemia frequently occurs. They have also been found in human medullary carcinoma of the thyroid where serum calcium levels are normal despite large amounts of calcitonin.

In a third variety of hypercalcemia, hypophosphatemia and low tubular reabsorption of phosphate (TRP) are present. This is now known to result from the elaboration of parathyroid-like hormone(s) by non-parathyroid cancers. This syndrome was postulated by Fuller Albright in 1941 because the *low* serum phosphate level could not be explained by excessive breakdown of bone. Twenty-five years later, his hypothesis was confirmed by direct immunoassays of parathyroid hormone (PTH) in malignant tissues and in blood. The laboratories of Tashjian et al, Sherwood et al, and Berson and Yalow, and our own laboratory, have confirmed the production of parathyroid-like hormone(s) by cancers of lung, kidney, colon, ovary and cervix. Berson and Yalow, and we too, have extended Albright's observation to show that PTH is increased in the serum of many patients with cancer but without hypercalcemia.[1,2]

Clinically, the hypercalcemia which results from the direct invasion of bone or from humoral processes may be compounded and exaggerated by immobilization, by dehydration, and by thiazide therapy. Prophylactic hydration and ambulation have proved effective in reducing the frequency of hypercalcemia in cancer patients.

The less common variety of hypercalcemia in which PTH is elaborated by malignant neoplasms is signaled by a low serum phosphate level and a low TRP. Caution must be observed in interpreting phosphate abnormalities in patients receiving glucose infusions or corticoids, either of which lowers the serum phosphate level. Thus hypophosphatemia in a hypercalcemic patient receiving glucose or corticoids does not necessarily indicate that the hypercalcemia is due to hyperparathyroidism.

Direct measurement of PTH is of help. Using both a chicken antiserum and a guinea pig antiserum developed against bovine PTH in a radioimmunoassay, we found identical reactivities of these antisera to the peptides extracted from the

parathyroid glands or in sera from patients with either primary hyperparathyroidism or the secondary hyperparathyroidism of uremia. They also react equally to the synthetic amino terminal 1-34 amino acid peptide (the biologically active sequence). In the sera of 11 patients with hypercalcemia and malignant disease *other than breast carcinoma,* the guinea pig antiserum detected immunoreactive PTH which the chicken antiserum did not. In three other sera, the chicken antiserum recognized material which the guinea pig did not. In none of the sera from patients with malignant disease and hypercalcemia did the two antisera detect immunoreactive PTH equally.[1,2] This shows that the ectopically produced PTH is immunologically different from that of the normal, adenomatous or hyperplastic parathyroid gland. Riggs et al[4] confirmed and extended this observation and reported the radioimmunoassay helpful in differentiating primary from ectopic hyperparathyroidism.

Establishing the cause of hypercalcemia in a patient with cancer poses a particular problem. Hypercalcemia may arise from the cancer by one of the mechanisms listed above, or it may arise co-incidentally—for example, from a parathyroid adenoma. It is, therefore, important to know that certain cancers are not associated with ectopic elaboration of parathyroid hormone. Of these, the most important is breast cancer, for these reasons: 85 percent of patients who have it ultimately show osseous metastasis, it is the cancer most commonly associated with hypercalcemia and it does *not* elaborate PTH. The hypercalcemia of breast cancer is usually but not always associated with osteolytic metastasis and in our experience is not associated with a low serum phosphate level or low TRP unless artifactually induced by glucose or corticoid administration. Thus the presence of hypercalcemia, hypophosphatemia and low TRP in a patient with breast cancer indicates an additional diagnosis. The diagnosis of co-incidental parathyroid adenoma in disseminated breast cancer has been verified to our knowledge in 16 patients. This association should be borne in mind, since neither breast cancer nor hyperparathyroidism is a rare condition and the combination is statistically far from unlikely.

The prognosis of hypercalcemia depends on the intensity of the process, the speed with which it is recognized, and the vigor with which it is treated. Most hypercalcemias of cancer respond well to relatively simple measures, such as hydration or corticoids. In patients who respond to treatment, the prognosis is that of the underlying disease, rather than of the hypercalcemia. Thus some women with indolent metastatic breast cancer may live comfortably for years if their hypercalcemia is corrected.

The report (printed elsewhere in this issue of CALIFORNIA MEDICINE) of two cases of hepatoma with hypercalcemia and hypophosphatemia illustrates several points. First, hypercalcemia of considerable degree may be present without lethargy. Weight loss may occur in patients with primary hyperparathyroidism due to anorexia, but losses in weight greater than ten pounds are more frequent with cancers. The need to consider hypercalcemia in each patient with malignant disease is emphasized.

Although hepatoma is an infrequent cause of death (three of every thousand autopsies) and hypercalcemia has not been a prominent part of its clinical picture, the increasing number of reports of ectopic production of parathyroid hormone by hepatomas suggests that this possibility should be considered in each patient with hepatoma. Direct measurement of PTH has been made in only one case,[5] but other clear-cut instances of ectopic production of PTH by hepatomas have been recorded as reported and reviewed in this issue. Presence of phytosterols in animal hepatomas has been noted, but the potent osteolytic short-chain esters of stigmasterol and Δ-7 sitosterol were not specifically looked for, nor have prostaglandins or other osteolytic humors been sought. It is clear that almost all malignant lesions can affect the host by elaboration of many humors. Knowledge of the pathophysiology of the hypercalcemia or malignant disease is progressing rapidly. Patient care can only benefit.

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